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Common Poisonings in Small Animals Mini Series

Session Two: Common Nephrotoxins and What To Do about Them

Shailen Jasani MA VETMB MRCVS DACVECC

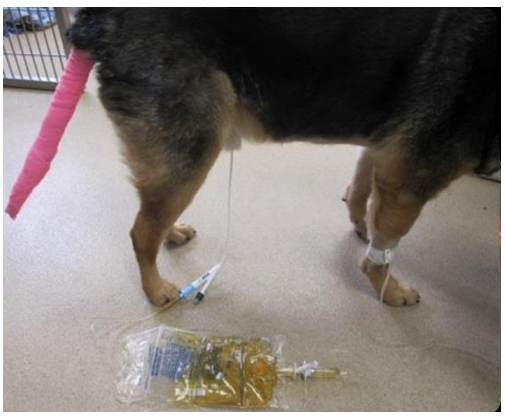


Table of Contents

Nephrotoxins

A general approach to the management of the acute kidney injury (AKI) caused by these various nephrotoxins is presented at the end of this section with poison-specific information included under the individual poison headings.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in human and veterinary medicine as both prescription-only and over-the-counter (OTC) preparations. A large heterogeneous variety of agents exists but they share certain therapeutic anti-inflammatory, antipyretic and analgesic effects as well as undesirable adverse effects. The following discussion presents general information about NSAID intoxication.

Toxic dose

The pharmacokinetics of NSAIDs show differences between species and doses used in people should not be extrapolated to dogs and cats. Unfortunately there is relatively little published information about toxic doses of NSAIDs in dogs and cats. As always, check with poisons information resources for the most recent information.

Toxic doses of some agents in the context of an acute* single overdose are reported as follows:

[* Toxic doses with chronic use may often be much less.]

NSAID	TOXIC DOSE	
	Dogs	**Cats**
Ibuprofen	100-125 mg/kg: vomiting, diarrhoea, nausea, abdominal pain, anorexia possible 175-300 mg/kg: renal failure possible > 400 mg/kg: CNS signs + renal and gastrointestinal > 600 mg/kg: considered lethal	Lower doses than for dogs, potentially 50% lower
Carprofen	> 20 mg/kg: gastrointestinal signs > 40 mg/kg: nephrotoxicity	> 4 mg/kg: gastrointestinal signs > 8 mg/kg: nephrotoxicity
Naproxen	Literature reports: • 35 mg/kg single dose • 11.11 mg/kg/day for 3 days • 5.6 mg/kg/day for 7 days	Lower doses than for dogs No published reports
Deracoxib	> 10 mg/kg: gastrointestinal toxicity possible > 20 mg/kg: nephrotoxicity + gastrointestinal	Lower doses than for dogs No published reports

Other resources should be consulted for information about other agents. Lower doses may be toxic for example in animals with pre-existing renal disease and also bear in mind that this type of information is derived from cases that were presented for treatment so it may be that lower doses than those listed can be toxic. A conservative “better safe than sorry” approach is recommended.

Toxicokinetics, Mechanism of toxicity

The effects of most NSAIDs are related to the impairment of prostaglandin production; there may be other important mechanisms, some not fully understood. Prostaglandin inhibition involves **cyclooxygenase (COX)** of which there are (at least) two types and the traditional dogma has been as follows:

COX-1 (constitutive, housekeeping)
- Variably found in all tissues
- Involved in the production of prostaglandins that are essential for a variety of normal functions

COX-2 (inducible)

- Levels typically very low but increase during tissue injury
- Primarily responsible for the production of prostaglandins that mediate the inflammatory response and pain associated with tissue injury

More recently it has been suggested that the traditional description above is too simplistic and that there is some overlap in the roles of COX-1 and COX-2. For example COX-2-mediated prostaglandins are thought to be vital for normal renal physiology and may also play a role in the healing of some tissues, especially the gastrointestinal tract. Some COX-1-mediated prostaglandins may be involved in the pain pathway.

Most NSAIDs are COX inhibitors. Some agents (e.g. carprofen, meloxicam) have more selective inhibition of COX-2 versus COX-1 (i.e. COX 1-sparing, 'preferentially selective') and are reportedly associated with fewer side effects and a safer therapeutic index than the older NSAIDs were. Even newer agents (e.g. firocoxib, cimicoxib, robenacoxib) are said to be COX-2 specific inhibitors (coxibs). However there is disagreement in the literature with respect to the selectivity of different NSAIDs for COX-1 versus COX-2. For the reason described above, it is likely that the significance of COX-1 versus COX-2 specificity in terms of the safety of an individual NSAID varies between tissues/organs depending on what role this enzyme plays in the health and healing of that tissue or organ. For example the gastrointestinal tract is highly COX-1 dependent for health so agents with greater COX-2 selectivity may be associated with fewer GI side-effects. COX-selectivity has no effect on analgesic efficacy.

NSAIDs are generally absorbed rapidly and almost completely following oral exposure; peak plasma concentration generally reached 2-4 hours following ingestion. Metabolism is usually hepatic with metabolites being mainly excreted in the urine. The major mechanism of conjugation is via glucuronidation; cats are especially sensitive to NSAID toxicosis because they have a limited glucuronyl-conjugating capacity. A number of NSAIDs undergo enterohepatic circulation. Elimination half-lives of NSAIDs vary widely from as little as 1 hour to as much as 50 hours depending on the individual agent; half-life is likely to be prolonged in patients with renal or hepatic disease, as well as in neonates.

Adverse effects of NSAIDs have been reported to predominantly involve the gastrointestinal tract, the kidneys, coagulation, and the liver. Adverse effects associated with NSAIDs are more likely to occur in animals exposed to excessive dosages as well as in those with volume depletion, hypotension or pre-existing gastrointestinal or renal disease. Bleeding tendency may be more common in animals with other concomitant coagulation abnormalities (e.g. von Willebrand's disease).

Gastrointestinal tract:

Gastrointestinal injury is the most common adverse effect associated with excessive NSAID exposure in dogs and cats. Gastroduodenal injury may occur following NSAID administration due to direct irritation of the mucosa (most NSAIDs are slightly acidic) and/or prostaglandin inhibition. Prostaglandins are important for the integrity of the gastrointestinal mucosal barrier (mucosal cytoprotection) and their impaired production therefore increases the likelihood of mucosal injury (haemorrhage, erosions, ulceration) in an already compromised tissue.

Kidneys:

Prostaglandins play an important role in the kidneys in modulating the tone of blood vessels and regulating salt and water balance. The kidney depends on COX-1 and COX-2 for prostaglandin synthesis to autoregulate water metabolism, tubular function, and renal blood flow. Prostaglandins are not critically involved in renal haemodynamics in normal healthy animals. However, in response to a decrease in renal blood flow, locally-acting prostaglandins serve to protect renal perfusion by exerting a compensatory vasodilatory effect. Their inhibition by NSAID therapy can therefore result in renal ischaemia and insufficiency. This is applicable to both older NSAIDs and newer agents with more selective COX-2 inhibition as constitutive COX-2 is produced in the kidney.

Thus nephrotoxicity and consequent renal insufficiency may occur in animals that are exposed to NSAIDs while in a state of volume depletion or hypotension as well as following exposure to massive overdose. Pre-existing renal disease at the time of overdose may clearly exacerbate the kidney injury.

Coagulation:

NSAIDs can induce coagulopathy by inhibiting COX within platelets and thereby impairing the production of thromboxane. Among other functions thromboxane facilitates platelet aggregation.

Hepatic injury is not a prominent feature of acute NSAID intoxication but may occur with some NSAIDs causing dose-dependent hepatotoxicity (e.g. aspirin, paracetamol (acetaminophen)).

Clinical signs

Early clinical signs of NSAID intoxication are likely to develop within a few hours and reflect gastrointestinal complications – vomiting, with or without haematemesis, and diarrhoea, with or without melaena (or haematochezia); inappetence, lethargy, depression, weakness and possible abdominal pain may occur. Dehydration and potentially hypovolaemia may be present. Cats may show gastrointestinal signs less frequently but tachypnoea may be more common than in dogs. In severe cases gastrointestinal perforation may occur with subsequent peritonitis that may be accompanied by abdominal pain and severe cardiovascular compromise. Animals may also present with oliguric or polyuric acute renal failure. Renal failure may be delayed for up to 5 days following exposure.

It is noteworthy that some NSAID preparations contain xylitol and theoretically this could cause/contribute to toxicity in dogs.

Laboratory and other tests

Depending on the time elapsed since ingestion clinicopathological findings may reflect gastrointestinal blood loss, with anaemia and possible panhypoproteinaemia. Anaemia may be pre-regenerative or regenerative. Pre-renal azotaemia may be identified and urea may be disproportionately elevated compared to creatinine due to gastrointestinal haemorrhage. Renal insufficiency will likely manifest as azotaemia, hyperphosphataemia, possible hypercalcaemia and isosthenuria. Proteinuria may also be detected.

If gastrointestinal perforation and peritonitis are suspected, additional testing is mandatory. Abdominal radiography may show loss of serosal detail due to free peritoneal fluid, and free peritoneal gas. Abdominal ultrasound may reveal free peritoneal fluid and may be used to guide abdominocentesis. Alternatively blind abdominocentesis may be performed although the use of ultrasound to detect peritoneal fluid and guide aspiration is highly recommended. Any fluid obtained should be examined cytologically and will typically be consistent with a purulent exudate if perforation has occurred.

Treatment

Depending on the time elapsed since ingestion, routine gastrointestinal decontamination including the use of activated charcoal may be indicated to minimise further drug absorption; activated charcoal should not be used however if other oral therapies are going to be used as it will likely impair their absorption. Intravenous fluid therapy using an isotonic crystalloid solution is indicated to correct hypovolaemia or dehydration (recurrence of fluid deficits must be prevented to minimise the risk of nephrotoxicity) and to promote renal toxin excretion. Animals exposed to nephrotoxic doses of NSAIDs should generally be kept on intravenous fluids for 2-4 days with monitoring of renal function.

Medical therapy designed to minimise further gastrointestinal compromise and to promote healing of injured, including potentially ulcerated, mucosa should be provided. Gastroprotectants may be needed for 7-14 days depending on the dose of NSAID exposure and the severity of clinical signs. Routine use of anti-emetics may be required.

Monitoring should be tailored to the individual patient but often includes hydration and renal parameters.

Medical therapy for nonsteroidal antiinflammatory agent (NSAID) intoxication [C – cats, D – dogs]:

Drug	Dose	Comments
Misoprostol	Dogs: 2-7.5 µg/kg per os every 8-12 hours Cats: 5 µg/kg per os every 8-12 hours	Synthetic prostaglandin analogue with multiple effects including reducing gastric acid secretion and cytoprotection Highly effective; treatment of choice Contraindicated in pregnant animals Wear gloves; women of childbearing age to take extra precautions May cause diarrhoea and/or abdominal cramps Previously 'not recommended' in cats but now gaining increasing experience
Omeprazole	Dogs, cats: 0.5-1 mg/kg slow IV, per os every 24 hours	Proton pump inhibitor thereby suppressing gastric acid production non-competitively and irreversibly; probably more effectively than (H_2) receptor antagonists May enhance prostaglandin activity conferring cytoprotective properties Maximum 3 days intravenous use
Famotidine	Dogs: 0.5-1 mg/kg per os, SC, IV every 12-24 hours Cats: 0.5-1 mg/kg per os, SC every 12-24 hours	Histamine (H_2) receptor antagonist, increasing gastric acid pH by competitively inhibiting acid secretion Longer duration of action and fewer drug interactions than cimetidine Anecdotal reports of intravascular haemolysis following intravenous administration in cats
Ranitidine	Dogs: 0.5-2 mg/kg slow IV every 8-12 hours; 1-2 mg/kg per os every 12 hours Cats: 2.5 mg/kg slow IV every 12 hours; 3.5 mg/kg per os every 12 hours	Histamine (H_2) receptor antagonist, increasing gastric acid pH by competitively inhibiting acid secretion Preferred over cimetidine as fewer drug interactions and less frequent dosing
Cimetidine	Dogs, cats: 5-10 mg/kg per os, slow IV every 6-8 hours	Histamine (H_2) receptor antagonist, increasing gastric acid pH by competitively inhibiting acid secretion Inhibits hepatic microsomal enzymes and may alter metabolic rates of other drugs (e.g. benzodiazepines, beta-blockers) Newer agents (e.g. ranitidine, famotidine) more effective, fewer drug interactions and longer dosing interval Other agents (e.g. omeprazole) more effective
Sucralfate	Dogs: 0.5-2 g per os every 8-12 hours Cats: 0.25 g per os every 8-12 hours	Coats ulcerated/exposed mucosa and promotes re-epithelialisation Less effective than misoprostol and omeprazole Administration 30- 60 minutes before food is recommended Tablets can be crushed and mixed with water

Surgical intervention is required in animals with gastrointestinal perforation and standard management of acute renal failure is indicated in appropriate cases.

Intravenous lipid emulsion?

NSAIDs vary with respect to how lipophilic they are depending on their chemical structure but some are said to be highly lipophilic; this may make ILE a consideration in the management of these patients, perhaps only in cases of massive exposure. To the author's knowledge the case report below is the only veterinary publication to date and no references were found in a brief search of the human literature. It is noteworthy that the Veterinary Poisons Information Service in the UK has been known to recommend ILE use in cases of significant NSAID intoxication, potentially on the basis of this case report, although we must remember that a single published case report is far from robust evidence.

Bolfer L, McMichael M, Ngwenyama TR, O'Brien MA. Treatment of ibuprofen toxicosis in a dog with IV lipid emulsion. J Am Anim Hosp Assoc 2014. 50(2):136-140.

"A 3 yr old spayed female mixed-breed dog weighing 19.4 kg was evaluated for ingestion of 1,856 mg/kg (180 tablets) of ibuprofen, a human formulated nonsteroidal anti-inflammatory drug (NSAID). At the time of presentation, the patient was alert and hypersalivating, but her mental status rapidly declined to obtunded, stuporous, and then comatose within 30 min of presentation. Initial treatment included supportive therapy with prostaglandin analogs and antiemetics. An IV lipid emulsion (ILE) was administered as a bolus, followed by a constant rate infusion. Clinical signs began to improve approximately 3 hr after completion of the lipid infusion. The patient required supportive care for 3 days before discharge. This case report demonstrates the use of ILE for treatment of ibuprofen toxicosis in a dog. ILE infusion may be a therapeutic option for patients with toxicosis due to lipid-soluble drugs."

Prognosis

The prognosis following NSAID poisoning is generally favourable if patients present early and can receive the necessary level of care. The prognosis is guarded with acute kidney injury but NSAID-mediated acute renal insufficiency is often reversible with adequate supportive care.

Aspirin

Aspirin is available as plain, film-coated, buffered, time-release, and enteric-coated tablets, suppositories, and capsules.It is noteworthy that in medicinal products aspirin is often found in combination with other potentially toxic substances, especially paracetamol (acetaminophen) and caffeine.

Toxic dose

In dogs aspirin administration at 50 mg/kg every 12 hours has been reported to cause vomiting, and haematemesis and gastric ulcer perforation have been reported at 100-300 mg/kg/day for 1-4 weeks. Acute ingestion at 450-500 mg/kg can cause signs of gastrointestinal disturbances, hyperthermia, panting, seizure, or coma in dogs. Due to deficiencies in aspirin metabolism, cats are more susceptible and the toxic dose is lower than for dogs; cats also have a much longer elimination half-life.

Toxicokinetics, Mechanism of toxicity

Aspirin (acetylsalicylic acid) is a synthetic NSAID. Following ingestion aspirin is readily absorbed and is then metabolised in the liver to salicylic acid. Some local hydrolysis to salicylic acid also occurs in the gastrointestinal tract. Salicylic acid is the active form and the form that is absorbed into the circulation. Elimination from the circulation depends on conjugation with glucuronic acid. At high dosages this conjugation becomes overwhelmed resulting in delayed clearance and accumulation of the active drug. Cats have a defective glucuronic acid conjugation system that results in prolonged drug elimination compared to dogs and an increased susceptibility to aspirin poisoning.

Clinical signs

Gastrointestinal irritation and injury are the most common adverse effects of aspirin ingestion and nephrotoxicity is also reported. Stimulation of the respiratory centre by salicylate results in hyperventilation and respiratory alkalosis and this is followed by a metabolic acidosis which is responsible for the majority of clinical signs. The metabolic acidosis in salicylate poisoning is a high anion gap acidosis. Severe and fatal acidaemia may occur within a few hours of aspirin ingestion.

Salicylate uncouples mitochondrial oxidative phosphorylation decreasing ATP production. There is also increased oxygen utilisation and increased production of carbon dioxide (contributes to hyperventilation) and lactate (contributes to metabolic acidosis).

Salicylates also have toxic effects in the CNS although the exact mechanism of toxicity is not known. Seizures have been reported in both dogs and cats secondary to salicylate toxicity. Non-cardiogenic pulmonary oedema is the most common cause of major morbidity in people and might be related to a salicylate-induced increase in the permeability of the pulmonary vasculature. Salicylates also inhibit vitamin K–dependent synthesis of coagulation factors (II, VII, IX, and X), leading to a prolonged prothrombin time, and inhibit prostaglandin-dependent platelet aggregation. Aspirin-induced hepatitis has also been reported in cats following excessive exposure.

Treatment

Treatment of aspirin poisoning is the same as described for other NSAIDs earlier. Sodium bicarbonate therapy may be needed if acidaemia is life-threatening; urine alkalinisation is often referred to but making sure that plasma alkalaemia is present should work fine and is practically more realistic.

Prognosis

Generally favourable if necessary care can be provided.

Ethylene glycol

Although ethylene glycol (EG) poisoning is a common cause of poisoning in companion animals in North America, its reported incidence is significantly lower in the United Kingdom. Ethylene glycol is a sweet-tasting liquid used primarily as an antifreeze, screen wash and windshield de-icing agent. It is now law in some states in North America that a bitter-tasting substance such as denatonium benzoate has to be added to antifreeze to try and reduce its palatability to animals. Efforts are underway to try and introduce something similar elsewhere in the world including in the UK where some progress has been made (e.g. http://www.capt.org.uk/who-we-are/news/Halfords--Prestone-add-Bitrex-to-products). Antifreeze ingestion is the most common source of EG poisoning with many common preparations containing as much as 95% ethylene glycol. Companion animal exposure is generally the result of environmental contamination from improper disposal or insecure storage and poisoning is most likely to occur in late autumn and early spring when antifreeze usage increases. Some people also use antifreeze in outdoor ornamental ponds to prevent freezing and animals may drink from these ponds.

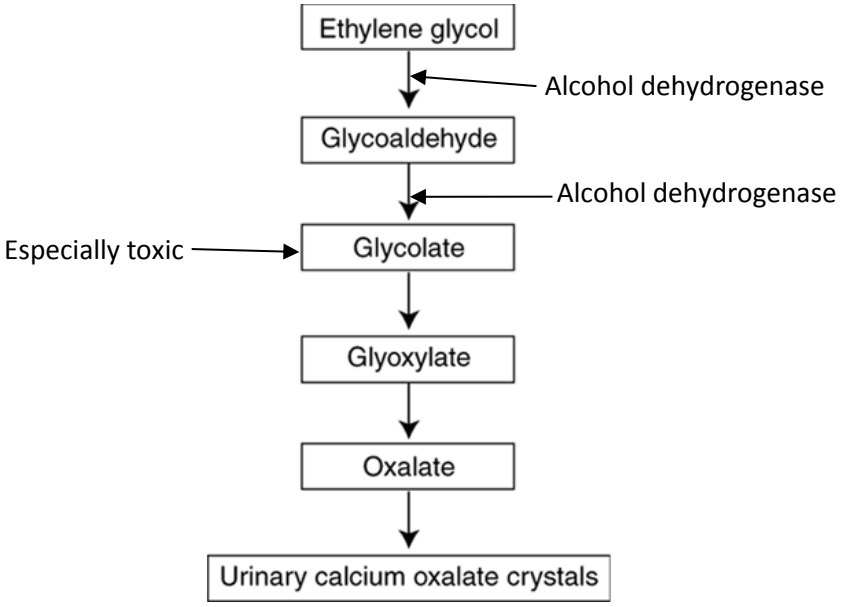
Toxic dose

The minimum lethal dose of undiluted EG is reported to be 4.4-6.6 ml/kg in dogs and 1.5 ml/kg in cats.

Toxicokinetics

Ethylene glycol is rapidly absorbed from the gastrointestinal tract and distributed systemically. Its plasma half-life is approximately 3 hours and a variable proportion is excreted unchanged in urine. The remainder is metabolised predominantly in the liver. The first step in this metabolism is oxidation of EG to glycoaldehyde by alcohol dehydrogenase (ADH), a conversion that can be saturated. Glycoaldehdye is then converted to glycolic acid (also involves ADH), glyoxylic acid and finally to oxalic acid. Ethylene glycol metabolic pathways may vary between species.

Calcium binds to oxalic acid resulting in the formation of calcium oxalate crystals that are deposited widely but especially in the renal tubules and calcium oxalate crystalluria is a common finding.



Mechanism of toxicity

The effects of ethylene glycol prior to metabolism are generally relatively minor. However the metabolites of EG are highly toxic. Acute renal failure is the most severe consequence of EG poisoning in companion animals. Most of the metabolites of EG are thought to be toxic to the renal tubular epithelium and calcium oxalate deposition may cause further damage.

Metabolism of EG generates free oxygen radicals that are potentially cytotoxic to a variety of tissues. In addition the organic acid metabolites produced interfere with normal cellular processes. Central nervous system dysfunction is thought to be predominantly due to the effects of glycoaldehyde along with calcium oxalate deposition in nervous tissue. Hypocalcaemia secondary to binding of calcium to oxalic acid and metabolic acidosis both may contribute further to CNS signs. Metabolic acidosis may be severe and is due to the accumulation of acid metabolites most notably glycolic acid.

Clinical signs

Clinical signs of EG poisoning are dose-dependent and in companion animals occur in **two phases**. The *first* is predominantly associated with EG itself prior to metabolism. Signs develop within an hour of ingestion and may persist for 12 hours. They include central nervous system depression, somnolence, ataxia, impairment of conscious proprioception, nausea, vomiting, and osmotic diuresis with consequent polyuria/polydipsia. In severe cases seizures, coma and death may occur. In dogs these signs may seemingly resolve with apparent recovery although they may occur earlier and be more persistent in cats.

The second phase of clinical signs is associated with the highly toxic metabolites of EG and is predominantly related to acute renal failure. Signs usually develop within 24-72 hours of ingestion in dogs, often earlier in cats, and may include reduced mentation from depression through to coma, seizures, anorexia, vomiting, and oliguria with low urine specific gravity or isosthenuria. Anuria may develop 3-4 days post-ingestion.

An intermediate phase between the two phases already described consists of cardiopulmonary manifestations (tachycardia, tachypnoea, pulmonary oedema) but this is recognised much less commonly in dogs and cats than in people.

Laboratory tests

Biochemistry, Acid-base analysis:

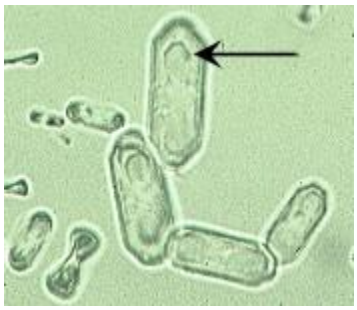
Early changes are mainly due to accumulation of acid EG metabolites with normochloraemic metabolic acidosis, reduced plasma bicarbonate (HCO_3^-) and increased anion gap. If plasma HCO_3^- measurement is not available, reduced concentration may be reflected as a decrease in total carbon dioxide (total CO_2). These changes may be detectable 1-3 hours following ingestion and a high anion gap may persist for 12-48 hours. Total hypocalcaemia may occur due to chelation by oxalic acid, hyperglycaemia is also reported, and pre-renal azotaemia may be detected with appropriately severe dehydration.

Later biochemical abnormalities reflect renal injury and reduced glomerular filtration rate with renal azotaemia and hyperphosphataemia. These changes are usually detectable 24-72 hours post-ingestion in dogs and earlier in cats.

Urinalysis:

Osmotic diuresis and polydipsia (due to increased serum osmolality) result in reduced urine specific gravity typically within 3 hours of EG ingestion. Dogs are usually isosthenuric (urine specific gravity 1.007-1.015) but urine specific gravity may be higher than this and often is in cats. Urine specific gravity remains low as renal insufficiency and impaired ability to concentrate urine develop in the later stages. Glucosuria with concurrent normoglycaemia may be detected in dogs as a result of proximal renal tubular damage.

Calcium oxalate crystals may be identified in urine 3-6 hours after EG ingestion. Calcium oxalate monohydrate crystals (clear six-sided prisms or dumbbell-shaped crystals) are more common than the dihydrate form (envelopes or Maltese cross-shaped).



Calcium oxalate monohydrate

Calcium oxalate dihydrate

Aciduria, haematuria, renal epithelial cells and casts are other common urinalysis findings. Casts are a mixture of mucoprotein and the trapped contents of the renal tubular lumen. They originate from the distal convoluted tubule or collecting duct during periods of urinary concentration or stasis, or when urinary pH is very low. Their cylindrical shape reflects the tubule in which they were formed and is retained when the casts are washed away. The predominant cellular elements determine the type of cast: hyaline, erythrocyte, leukocyte, epithelial, granular, waxy, fatty, and mixed.

Plasma ethylene glycol concentration:

Plasma EG concentrations peak 1-6 hours post-ingestion and EG is usually no longer detectable in plasma (or urine) by 48-72 hours post-ingestion. Ethylene glycol test strips are available, although potentially not worldwide. They are sold in the UK by Woodley Veterinary Diagnostics by whom the following information is provided:

"These [colour change] test strips report quantitative results for Ethylene Glycol in plasma. Providing critical information on exposure to this toxin for both Canine and Feline in as early as 30 minutes after ingestion.

- Feline sensitivity at 20 mg/dl [Note comment above regarding the higher minimum detectable level of the test kits potentially making them less useful for cats.]
- Canine sensitivity at 50 mg/dl
- Only 20 µl of plasma required
- Detects Ethylene Glycol 30 minutes after ingestion
- Results in 10 minutes
- Long expiration date"

[2012: A box of 5 costs £85.]

A commercial test kit (Ethylene Glycol Test Kit®, PRN Pharmacal Inc, Florida; www.prnpharmacal.com/egtkit/index.php) used to be available for estimating serum EG concentrations based on an enzymatic assay; it was both accurate enough for clinical use and relatively inexpensive. Results were available within 30 minutes. These kits had a minimum detectable level of 50 mg/dl of EG in the blood and it is noteworthy that cats may develop clinically significant poisoning despite serum EG levels lower than this threshold. These kits have now been discontinued.

The EG test kit may generate a false-positive result if propylene glycol or glycerol is present in the patient's blood. Propylene glycol is a constituent of some activated charcoal suspensions, diazepam formulations and semi-moist diets. Blood for this test should be drawn before administration of any preparations that may contain propylene glycol or glycerol. False-positive results may also occur following metaldehyde ingestion but do not occur in the presence of ethanol.

Serum osmolality:

Ethylene glycol is an osmotically active substance and ingestion results in an increase in serum osmolality and osmole gap (equivalent to the measured serum osmolality minus the calculated osmolality). Measurement of serum osmolality is useful for identifying early EG poisoning. However access to measured serum osmolality is likely to be very limited in general emergency practice.

Wood's lamp:

A number of modern antifreeze preparations contain sodium fluorescein to aid in detection of radiator leaks. This dye is excreted in urine for up to 6 hours or more following ingestion. Urine as well as the mouth, paws and vomitus can therefore be examined with a Wood's lamp (or similar) for fluorescence due to the presence of this dye. However it is noteworthy that a negative result does not exclude the possibility of EG ingestion as not all antifreeze preparations contain sodium fluorescein. Furthermore, false positives may occur as a large number of drugs and other substances can cause fluorescence under a Wood's lamp.

Treatment

Treatment of suspected EG poisoning should be instituted as early as possible because it is metabolised rapidly into highly toxic metabolites. Treatment consists of the following components:

- Gastrointestinal decontamination to minimise EG absorption
- Preventing metabolism of absorbed EG to more toxic metabolites
- Promoting urinary excretion of EG and its metabolites with intravenous fluid therapy
- Correction of fluid, acid-base and electrolyte abnormalities
- Supportive/nursing care

Gastrointestinal decontamination:

Ethylene glycol is absorbed very rapidly from the gastrointestinal tract and GID may therefore only be of benefit very early post-ingestion (1-2 hours). Activated charcoal decreases ethanol absorption and should not therefore be administered if oral ethanol is being used as an antidote.

Preventing ethylene glycol metabolism:

The prevention of EG oxidation by ADH is the most important component of therapy and may be achieved in one of two ways, inhibition of the enzyme or provision of a competitive substrate. Treatment should be administered in all animals presenting within 36 hours of EG ingestion.

Every attempt should be made to initiate fomepizole or ethanol therapy as soon as possible following exposure as time is very much of the essence and the time to initiation of therapy is the predominant determinant factor affecting prognosis.

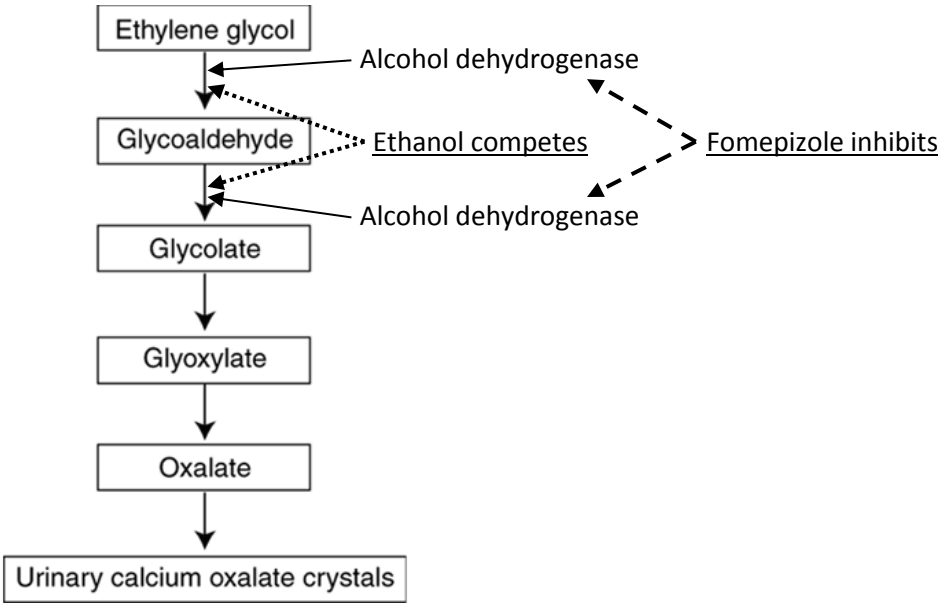
Fomepizole:

Alcohol dehydrogenase may be inhibited by the administration of fomepizole (4-methylpyrazole, 4-MP). This agent is a synthetic competitive ADH inhibitor and has become the treatment of choice in EG poisoning – however its veterinary use may be restricted by lack of availability e.g. in the UK. Minimal side effects have been reported following the use of this agent in companion animals and in particular it lacks the central nervous system depressive effects of ethanol (see below).

Dosing guidelines:

DOGS	
First dose	20 mg/Kg IV
12 hours after first dose	15 mg/kg IV
24 hours after first dose	15 mg/Kg IV
36 hours after first dose	5 mg/Kg IV
Every 12 hours thereafter give 5 mg/Kg IV until recovery occurs	

CATS	
First dose	125 mg/Kg IV
12 hours after first dose	31.25 mg/kg IV
24 hours after first dose	31.25 mg/Kg IV
36 hours after first dose	31.25 mg/Kg IV
Every 12 hours thereafter give 31.25 mg/Kg IV until recovery occurs	



Ethanol:

Ethanol may be used in the treatment of EG poisoning as it has a higher affinity for ADH than EG and therefore acts as a preferential competitive substrate. Injectable ethanol should be diluted in saline prior to administration. If a pure preparation for injection is not available, ethanol may be administered using an alcoholic beverage.

Dosing guidelines – injectable 20% ethanol:

DOGS: 5.5 mL of 20% ethanol/Kg IV every 4 hours for 5 doses then every 6 hours for 4 doses; or, give the same total dose over the same period as a constant rate infusion.

CATS: 5.0 ml of 20% ethanol/Kg IV every 6 hours for 5 doses then every 8 hours for 4 doses; or, give the same total dose over the same period as a constant rate infusion.

Injectable ethanol should be diluted in saline prior to administration

Dosing guidelines – 40% alcoholic beverage:

If a pure ethanol preparation for injection is not available, it may be administered orally or indeed intravenously using an alcoholic beverage.

DOGS: 4.4-6.6 ml/Kg of 40% ethanol alcoholic beverage per os – or IV – every 4 hours for 5 doses then every 6 hours for 4 doses

CATS: 4.4 ml/Kg of 40% ethanol alcoholic beverage per os – or IV – every 6 hours for 5 doses then every 8 hours for 4 doses

Perhaps the biggest disadvantage of the therapeutic use of ethanol is the associated central nervous system depression that may necessitate intensive and supportive care, especially with intermittent bolus administration and in cats. If oral ethanol is being used direct administration via orogastric intubation may prove necessary in animals that are too sedate to swallow reliably.

Given the treatment implications it can sometimes be hard to be convinced that starting ethanol treatment is appropriate in cases where the index of suspicion of ethylene glycol intoxication is minimal/low; and yet early antidotal therapy is really the only hope for survival in cases that have been exposed to a toxic dose so is a liberal approach to starting ethanol treatment justified? Not a comfortable conundrum to resolve!

Other ethanol-containing preparations such as surgical spirit or methylated spirits should be avoided as they contain methanol. Ethanol should not be administered to animals presenting in renal failure as ingested EG will already have been metabolised by that stage.

Other treatment considerations:

Appropriate supportive therapy consists of intravenous fluid therapy to correct hypovolaemia and dehydration and to promote diuresis. Potassium and calcium supplementation should be provided as deemed necessary on the basis of regular monitoring. Patients presenting with oliguric renal failure should be treated with intravenous fluid therapy and diuretic agents to establish diuresis if possible. If adequate diuresis cannot be established then referral for haemodialysis or peritoneal dialysis should be considered if available and affordable.

Renal tubular damage caused by EG may be reversible but can take weeks to months and urine concentrating ability may never return in some cases. Most dogs and cats surviving the acute renal failure phase of EG poisoning will eventually regain normal renal function.

Patients suffering from EG poisoning may be severely depressed and recumbent both from the poisoning and from treatment if ethanol is used. Standard nursing measures for recumbent patients should be implemented including provision of clean dry well-padded bedding, regular turning and bladder management. Regular eye lubrication and oral care may be needed and patients must be monitored closely for hypothermia.

Prognosis

Prognosis depends on the dosage of EG ingested, rate of absorption and **most importantly the *time to institution of specific therapy***. A reasonable summary of the little literature available at this time is probably as follows:

- The prognosis for dogs is reasonable-to-good if treated with fomepizole or ethanol within 8 hours of exposure
- The prognosis for cats is in general worse than for dogs but is nevertheless considered good if treatment can be initiated within 3 hours of exposure and is still reasonable within 8 hours of exposure
- Fomepizole is likely to be more effective than ethanol

A grave prognosis for survival is heralded by the onset of oliguric renal failure in both species and unfortunately most animals present at this late stage. Some – potentially only a small amount – recovery of renal function may be possible with dialysis which may need to be (very) long-term.

[NB. The author also came across this product which contains the DeTox® additive. DeTox® reportedly prevents ethylene glycol from being metabolised – the author is unsure but it may be an alcohol dehydrogenase inhibitor. Tests carried out on Thermox DTX confirmed the toxicity was "so low that it was impossible to determine an LD50 value". The DeTox® additive has very little effect on heat transfer or antifreeze performance. Assuming all of this is true, the author is unclear why this additive is not more well-known!
http://www.hydratech.co.uk/uk/products/thermox-dtx-geothermal-&-air-source-fluid/25]

***Vitis* fruits (Grapes, raisins, currants, sultanas)**

Poisoning in dogs has been recognised since the late 1990s. No confirmed cases have been reported in cats at the time of writing but susceptibility is suspected. A similar syndrome has not been reported in people.

The same poisoning syndrome may occur following consumption of all types of these fruits including those manufactured organically and regardless of whether the product has been cooked or not. Based on current information, the potential for toxicity should be considered in all cases regardless of the dosage consumed. It is also important to remember that exposure may occur through ingestion of products containing these fruits amongst their ingredients such as some chocolates, cakes or grape jelly. Dried fruits may carry a greater risk.

Toxic dose, Toxicokinetics, Mechanism of toxicity

Ingestion may be associated with renal toxicity but the toxin or toxins involved have yet to be identified and the mechanism of toxicity is unknown. Thus far there does not appear to be a correlation between the quantity consumed and the subsequent renal pathology and clinical progression; an idiosyncratic reaction is suspected.

Clinical signs

Vomiting is reported in almost all cases, usually within 24 hours of ingestion, and fruits may be identified in the vomitus. Vomiting may be related to dietary indiscretion or the development of azotaemia, but a specific effect of these fruits is also suspected due to the frequency with which this sign is reported; haematemesis may occur. Subsequently anorexia, lethargy, diarrhoea and abdominal pain have been reported as has hypersalivation.

Emergency database

Depending on the timeframe and severity, emergency database may demonstrate dehydration alone (increased PCV/TS) ± hypokalaemia secondary to vomiting; mild pre-renal azotaemia may also be present. Later, more severe azotaemia and hyperphosphataemia due to acute renal failure may be identified ± hyperkalaemia. Urinalysis may reveal isosthenuria, tubular casts, proteinuria and glucosuria.

Case management

Acute renal failure does not develop in all dogs following ingestion of these fruits. Nevertheless, as poisoning is suspected at this time to be due to an idiosyncratic non-dose related reaction the author recommends that treatment should be instituted in all cases following ingestion as early as possible – not everyone agrees with this recommendation. Gastrointestinal decontamination including induction of emesis if the animal is not already vomiting and administration of activated charcoal is performed and intravenous fluid therapy provided for a minimum of 48 hours; a typical rate is twice maintenance replacement isotonic crystalloid (i.e. this is not aggressive forced diuresis). Although a beneficial effect of fluid therapy on outcome has yet to be convincingly demonstrated, both the potential benefits (promoting toxin excretion, minimising tubular exposure etc.) of this therapy and the gravity of this poisoning syndrome make it a recommended treatment in all cases. Serum chemistry and urine output should be monitored for 72 hours.

Standard management for acute renal failure is indicated including appropriate intravenous fluid therapy, and diuresis if required using furosemide and/or mannitol. Mannitol should not be used in anuric animals. A soft in-dwelling urethral catheter attached to a closed collection system is ideal for monitoring urine output. Additional symptomatic therapy including antiemetics and gastroprotectants should be used. Antibiotics are not indicated and should be avoided as much as possible in animals with an in-dwelling urethral catheter – this practice is likely to select for more resistant and potentially more pathogenic bacteria.

If anuria/severe oliguria is present and is unresponsive to medical therapy, referral for peritoneal dialysis is required; haemodialysis is not currently available in the United Kingdom.

Outcome is not correlated with the dosage of fruits ingested. Prognosis is likely to be good with early treatment before the onset of renal impairment. The prognosis for survival following the onset of oliguric and in particular anuric acute renal failure is poor but some dogs may recover especially if dialysis is available. Clinical signs are expected to resolve fully in recovering dogs while blood renal parameters may or may not normalise. Normalisation of renal parameters, interpreted as adequate resolution of renal dysfunction, may take several weeks or months.

Lilies

Domestic cats are the only animals thus far reported to be susceptible to lily nephrotoxicity. Earliest reports involved Easter lily (*Lilium longiflorun*) but it is now suspected that all species of the *Lilium* genera, including Tiger lily, as well as day lilies (*Hemerocallis* genera) may be potentially nephrotoxic to cats. All parts of the plants including the flowers are associated with poisoning and exposure is usually via access to household plants.

Toxic dose, Toxicokinetics, Mechanism of toxicity

Even very small amounts of plant ingestion may be poisonous to cats and rapid absorption from the gastrointestinal tract is suspected as some cats still develop renal insufficiency despite early gastrointestinal decontamination. The toxin or toxins involved have yet to be identified and metabolism is unknown. The precise mechanism of toxicity is unknown but renal tubular epithelial necrosis and subsequent acute renal failure is known to occur. Pancreatitis and pancreatic degeneration have also been reported in cats with lily poisoning as have seizures of unconfirmed pathogenesis.

Clinical signs

Clinical signs may develop in as little as 5-10 minutes following ingestion and early signs are likely related to gastrointestinal effects. Within 1-6 hours vomiting, salivation, depression, lethargy and anorexia may be apparent. Polyuria and consequent dehydration occur 12-30 hours following ingestion and this is followed by anuria.

Anuria typically occurs 24-48 hours following ingestion and death may occur within 7 days of exposure. Renomegaly and abdominal pain may be detected in some cats.

Emergency database

Depending on the time elapsed since ingestion clinicopathological findings are likely to reflect acute renal failure with azotaemia, hyperphosphataemia and possible hyperkalaemia. These abnormalities are usually evident within 24-72 hours of ingestion. Urinalysis may reveal isosthenuria, tubular casts, proteinuria and glucosuria.

Case management

Depending on the time elapsed since ingestion, routine GID may be indicated to minimise absorption. Any pollen on the skin or fur should be washed off thoroughly. Fluid diuresis should be implemented for 24-72 hours with monitoring of hydration status, serum biochemistry and urinalysis; a typical rate is twice maintenance replacement isotonic crystalloid (i.e. this is not aggressive forced diuresis). Potential benefits of fluid therapy include promoting toxin excretion and minimising tubular exposure. Diuretic therapy (furosemide, mannitol) may be beneficial for maintaining fluid balance in cats with oliguric renal failure but is unlikely to induce urine production in anuric cats for whom referral for dialysis may be the only treatment option if available and affordable. Mannitol should not be used in anuric animals.

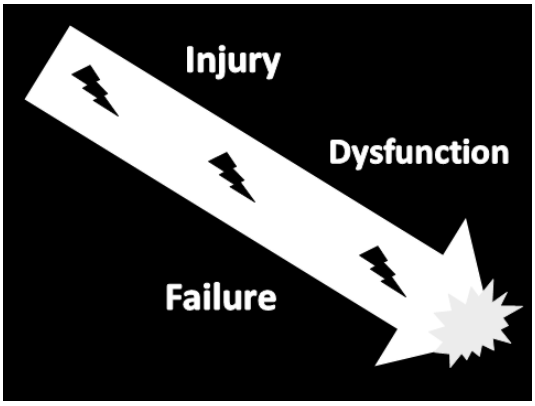
Prognosis

Prognosis depends in large part on the time between ingestion and presentation for treatment. Early presentation with GID and fluid diuresis carries a good prognosis for clinical recovery although some chronic renal dysfunction may persist. The prognosis is grave with standard medical therapy following the onset of anuria. The prognosis for anuric animals receiving dialysis may be favourable but remains to be elucidated.

General Approach to Acute Kidney Injury (AKI)

Relevant theory

In the past people used to only really refer to acute renal failure but more recently the term acute kidney injury (AKI) has been introduced. In essence the notion is that cellular injury may occur without resulting in overall renal dysfunction and similarly some degree of dysfunction does not necessarily constitute 'failure'.



Definition of AKI:

= Rapid (usually within 48 hours) reduction in renal function

In humans, AKI is recognised by:

- An increase in plasma creatinine
- A decrease in glomerular filtration rate (GFR)
- Or a reduction in urine output

To better emphasize the concept that AKI represents a continuum of renal injury, two staging schemes – the RIFLE scheme and the AKIN criteria – based around these criteria have been proposed for human patients to stratify the extent and duration of renal injury and predict clinical outcomes. There is considerable overlap between both systems. They have been adapted and applied retrospectively to dogs. In essence a higher grade is reportedly correlated with increased mortality but when applying such schemes to individual veterinary patients it is important to remember that the evidence base validating them remains minimal at this time. A scheme does not currently exist for cats.

It is also noteworthy that the criteria which define these staging schemes in humans are not as consistently applicable in animal patients with naturally occurring disease. In humans, AKI is a condition that manifests typically within the hospital setting. In animals, by contrast, AKI most commonly develops outside of the hospital setting and, as a consequence, the abruptness of the disease and the magnitude of changes in GFR, azotaemia, and/or urine production are rarely known or quantitated.

From Mugford A, Li R, Humm K. Acute kidney injury in dogs and cats 1. Pathogenesis and diagnosis. In Practice 2013. 35:253-364.

Table 1:
Classification schemes of acute kidney injury in dogs

Class	RIFLE creatinine / GFR criteria	Urine output criteria	AKIN class definition
Risk	Increase >150% of baseline GFR decreased by 25 to 50%	<0.5 ml/kg/hour for >6 hours	I. Serum creatinine increase of >26.5 µmol/l or 1.5 to 2.0x baseline
Injury	Increase >200% of baseline GFR decreased by 50 to 75%	<0.5 ml/kg/hour for >12 hours	II. 2 to 3x increase from baseline
Failure	Increase 300% of baseline GFR decreased by >75% or absolute increase in creatinine of 355 µmol/l or an acute increase of 44 µmol/l	<0.3 ml/kg/hour for >24 hours or anuria for 12 hours	III. >3x increase from baseline or >354 µmol/l or acute increase of 44 µmol/l
Loss	Persistent renal function loss >4 weeks		AKIN not applied
ESRD	End-stage disease >3 months		AKIN not applied

- AKIN Acute Kidney Injury Network, ESRD End-stage renal disease, GFR Glomerular filtration rate, RIFLE Risk, Injury, Failure, Loss and ESRD
- Adapted from Lee and others 2011 and Thoen and Kerl 2011*

[* Lee YJ, Chang CC, Chan JPW, et al. Prognosis of acute kidney injury in dogs using RIFLE (Risk, Injury, Failure, Loss and End-stage renal failure)-like criteria. Vet Rec 2011. 168:264.

Thoen ME, Kerl ME. Characterization of acute kidney injury in hospitalized dogs and evaluation of a veterinary acute kidney injury staging system. J Vet Emerg Crit Care 2011. 21:648–657.]

The International Renal Interest Society (IRIS) also produced an AKI grading system in 2013 intended for use in both dogs and cats. “The “grade” represents a moment in the course of the disease and is predicted to change as the condition worsens, improves, or transitions to CKD”. The full details of this system are beyond the scope of these notes but can be found online open access here.

Consequences of significant decrease in GFR include:

- Accumulation of uraemic toxins and metabolic waste products
- Dysfunctional fluid, electrolyte and acid-base homeostasis

One of the interesting points to note from the AKI schemes is that an increase in plasma creatinine from baseline is considered to be potentially significant even if creatinine still remains within the reference interval for that species and analyser. Clearly the same analyser needs to be used when measuring serial creatinine levels for trends to be interpreted.

Causes of AKI:

There are many possible causes of AKI in dogs and cats. They can be broadly classified as pre-renal, renal or post-renal.

Pre-renal causes involve decreased renal blood flow; the kidneys normally receive 20% of cardiac output making them especially susceptible to ischaemic (and toxic) injury. Decreased renal blood flow may be due to a localised problem but it is usually due to generalised hypoperfusion resulting from severe dehydration, hypovolaemia of other causes, or other forms of shock.

Prolonged decrease in renal blood flow may result in structural injury and irreversible intrinsic renal failure. It is essential to improve renal blood flow if possible before performing interventions that may predispose patients to further renal injury (e.g. general anaesthesia, nephrotoxic drugs).

Intrinsic renal causes involve direct renal parenchymal injury. The most common cause in companion animals are toxins, including nephrotoxic drugs, although it is noteworthy that in most cases the diagnosis is one of association (i.e. between a compatible history and the development of AKI) without definitive proof. In some cases, there is no compatible history and the diagnosis remains entirely presumptive.

Toxins associated with AKI in companion animals include grapes/raisins/currants/sultanas (dogs), lilies (cats), vitamin D (AKI due to hypercalcaemia), and ethylene glycol (antifreeze, dogs and cats). Drugs with the potential for significant nephrotoxicity include non-steroidal anti-inflammatory drugs and aminoglycoside antimicrobials, although a large number of other drugs have been implicated.

Other causes of direct renal parenchymal injury include infectious causes:

- Canine leptospirosis is a relatively common infectious cause of AKI
- Pyelonephritis may also cause AKI and most commonly occurs as a result of ascending lower urinary tract infection secondary to bacterial cystitis. Pyelonephritis may also occur secondary to haematogenous spread of bacteria.

AKI may also occur in syndromes such as heatstroke, sepsis and disseminated intravascular coagulation (DIC).
Other possible causes include hypertensive injury, neoplasia, non-ischaemic hypoxic injury and trauma.

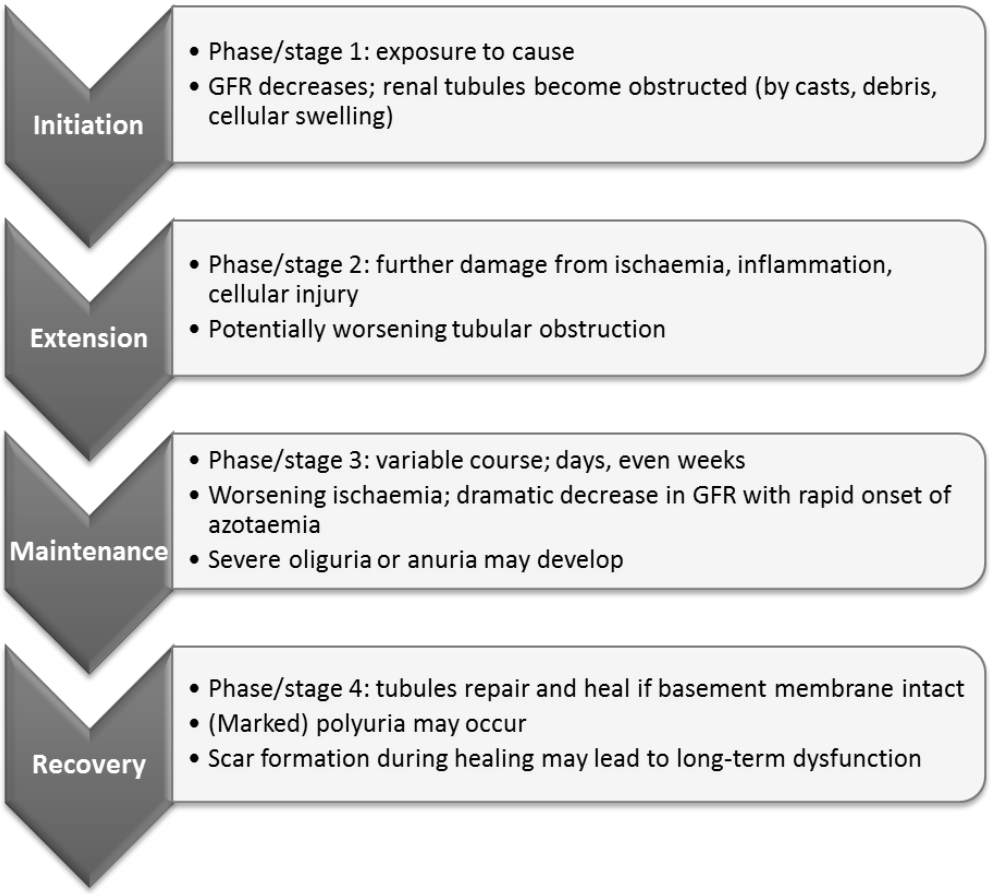
Post-renal causes of AKI involve pressure injury secondary to prolonged urinary tract obstruction. Although animals with post-renal abnormalities can have severe azotaemia, in most cases irreversible AKI does not occur if the cause is treated early.

In some cases the patient will have had chronic kidney disease (CKD) and then suffer AKI resulting in so-called acute-on-chronic kidney disease; causes of AKI more commonly implicated in such cases include pyelonephritis or obstructive urolithiasis but the acute deterioration may also be the result of rapid worsening of the cause of the CKD.

Common findings on initial presentation	**Acute kidney injury**	**Chronic kidney disease**
Body condition score	Normal	Decreased
Packed cell volume	Normal	Decreased (non-regenerative anaemia)
Renal size	Normal/increased	Normal/decreased
Thirst	Decreased/normal	Increased
Urine output	Decreased/increased	Increased
Abdominal pain	Present/absent	Absent
Uraemic ulceration	Initially absent	May be present
Soft tissue mineralisation	Absent	Present (end-stage)

(Modified from Mugford A, Li R, Humm K. Acute kidney injury in dogs and cats 1. Pathogenesis and diagnosis. In Practice 2013. 35:253-364.)

Pathogenesis:



Routine laboratory tests and clinical examination findings may not detect evidence of AKI during first two stages due to:

- Lack of baseline renal values (in many cases)
- Non-specific clinical signs (e.g. lethargy, inappetence, abdominal pain)

AKI generally detected in maintenance phase
Potentially marked polyuria in recovery phase may be due to osmotic diuresis secondary to medullary washout and/or incomplete recovery of tubular function

Conversion from oliguria or anuria to polyuria does not necessarily mean full functional recovery will occur; however it is an encouraging sign and also greatly facilitates patient management.

Clinical findings

History is often non-specific but it is very important to question carers with respect to potential exposure to toxins or drug overdoses in particular.

Clinical signs:

Non-specific signs such as inappetence/anorexia, lethargy, depression, vomiting, diarrhoea etc.
Polyuria/polydipsia may also be reported in CKD with acute injury

Physical examination:

Cardiovascular: may be normal or potentially consistent with hypovolaemia; tachycardia may also be due to e.g. pain, pyrexia

- Hypovolaemia may develop due to: dehydration from gastrointestinal loss and reduced intake; third-space losses due to hypoproteinaemia and/or capillary leakage depending on the underlying cause of AKI
- Hyperkalaemic patients may have bradycardia

Respiratory: may be normal or there may be tachypnoea from e.g. pain, pyrexia, metabolic status
Central neurological: mentation may be normal or reduced from depression through to stupor; seizures have been reported

Abdominal palpation may be painful and kidneys may be enlarged
Pyrexia may be present with pyelonephritis
Halitosis may be detected

Emergency database

Minimum emergency database:

Manual packed cell volume (PCV) may be increased due to haemoconcentration from dehydration

- Animals with acute-on-chronic kidney disease, may have chronic non-regenerative anaemia – may not be uncovered until adequate fluid resuscitation performed

Plasma total solids/protein (TS/TP) may also be increased due to haemoconcentration

- Albumin loss from protein-losing nephropathy may have some TS-lowering effect

Blood urea nitrogen (BUN) will be increased with renal +/- pre-renal azotaemia
Blood glucose is usually unremarkable

Extended emergency database:

Creatinine, electrolytes – especially potassium (both hyper- and hypokalaemia possible), sodium and calcium – and phosphorus should also be checked
If available, acid-base analysis may reveal variable metabolic acidosis due to reduced renal acid excretion and bicarbonate reabsorption

Diagnosis

Clinical pathology:

Diagnosis is made on the basis of **clinical pathology** findings:

Azotaemia of variable severity is expected and it is important to consider pre-renal and/or post-renal causes/contributions before assuming that the azotaemia is either renal or at least entirely renal in origin.
Isosthenuria (USG 1.007-1.015) is expected in a patient with intrinsic renal azotaemia – ideally check USG before starting fluid therapy but do not withhold fluid therapy in hypovolaemic patients

Urinalysis may also reveal:

- Casts suggestive of tubular injury +/- glucosuria suggestive of proximal tubular injury
- Evidence of (possible) infection – especially if bacteria are seen, culture and sensitivity testing should be performed
    - Note that even samples obtained by cystocentesis may culture negative despite bacterial pyelonephritis being present
    - Whether or not pyelonephritis is under-diagnosed remains unclear but is likely; the author is not aware of routine sampling for example under ultrasound guidance of fluid from the renal pelvis to aid in this diagnosis.
- Calcium oxalate crystals in ethylene glycol toxicity

Diagnostic imaging:

Diagnostic imaging – ultrasonography, plain +/- contrast radiography – is generally performed in patients with AKI both to evaluate kidney size, shape and structure, and to potentially identify causes, e.g. changes consistent with chronic renal disease or renal neoplasia – especially lymphoma; urolithiasis.

Fluid overload may result in renal pelvis dilation +/- retroperitoneal/peritoneal free fluid.

Other tests:

Other tests that may be indicated in individual patients include:

- Leptospirosis testing, especially PCR testing of blood and urine; at least in some parts of the world/in certain parts of individual countries, there is an argument for a liberal approach to testing for this disease.
- Ethylene glycol testing (if available) using colorimetric strips or test kits
- Screening for tick-borne and other infectious agents

Urinary biomarkers of AKI:

"Routinely, kidney dysfunction and decreased glomerular filtration rate (GFR) are diagnosed by the evaluation of changes in the serum creatinine (SCr) and blood urea nitrogen (BUN) concentrations. However, neither of these tests is sensitive or specific enough for the early diagnosis of impaired kidney function because they are both affected by other renal and nonrenal factors. Furthermore, kidney injury can be present in the absence of kidney dysfunction. Renal reserve enables normal GFR even when nephrons are damaged. Renal biomarkers, especially those present in urine, may be useful for the study of both acute and chronic nephropathies".

"Biomarkers are defined as biological variables that can be objectively measured and act as indicators of normal processes, pathological processes, or responses to intervention…The ideal biomarker for kidney injury should be able to (1) detect kidney injury at an early stage, (2) localize kidney injury (ie, at the glomerular level, tubular level, or both), (3) differentiate renal injury from pre-, post-, and nonrenal injury, (4) predict severity of renal injury, and (5) monitor the effects of intervention…To be clinically applicable, the biomarker should be accurate, easy to measure, and noninvasive….at different stages of AKI, it may be beneficial to evaluate different types of urinary biomarkers. Within the spectrum of kidney injury/dysfunction/failure, the early stage of kidney injury may be detected by early injury biomarkers whereas the later stages of kidney dysfunction/failure as diagnosed by routine functional biomarkers (eg, SCr, BUN) also may be detected by late injury biomarkers."

This text is from an open access review of urinary biomarkers for AKI in dogs which can be read here. In essence the thesis is that renal biomarkers may allow AKI to be detected earlier than using the current comparatively insensitive and late onset parameters of plasma BUN, plasma creatinine or urinary markers of tubular injury such as casts, glucosuria or proteinuria. Specific detection of glomerular injury, tubular injury, or both at an early stage (i.e. before GFR is decreased or before decreased GFR is detected by routine serum biomarkers) might permit earlier therapeutic intervention.

Further discussion of biomarkers is beyond the scope of these notes but some potential substances include:

- Albumin
- Immunoglobulin G
- Cystatin C
- Retinol-binding Protein
- Variety of tubular proteins (e.g. Kidney Injury Molecule-1 – see here for example)
- Variety of inflammatory proteins (e.g. Urinary neutrophil gelatinase-associated lipocalin (NGAL) – see here for example)

In 2014 Idexx also made available a test for measuring plasma symmetric dimethylarginine (SDMA) which is another renal biomarker that has been investigated.

Renal biopsy:

Depending on the cause renal biopsy may be useful from a diagnostic point-of-view. Mostly this would be with respect to neoplasia and fine needle aspiration rather than Trucut® needle biopsy or surgical biopsy may suffice, especially for example with renal lymphoma, and is less invasive.

Even if renal biopsy is not thought to be indicated diagnostically, can it help prognostically?

In many cases the answer to this question is likely to be 'yes' or at least 'maybe'. The renal basement membranes can be examined to see if they are completely denuded or there is some evidence of the potential to regenerate and recover. Some hurdles with the use of renal biopsy however are:

- Examination of the renal basement membranes for prognostic purposes requires specialist equipment and expertise that is not widely available; the author is to date only aware of one veterinary laboratory (Texas, USA) that offers this service. Courier service and a fast turnaround time are available.
- Costs: especially for UK-based practices, the cost implications of submitting samples for examination can be highly significant in decision-making. That said renal biopsy may prove cost effective if it saves on-going medical expenses in cases with a hopeless prognosis.
- Clinical application: to the author's knowledge there is very little information available from clinical patients correlating biopsy findings with progression and outcome; while a grave prognosis may be logical with terrible biopsy findings, how to correlate less severe findings with recovery of renal function and clinical progress remains unclear. Cases with some evidence of the potential for basement membrane regeneration may for example take weeks-to-months to regain adequate renal function – can the patient be supported adequately during this time with chronic intermittent haemodialysis, treatment that is not widely available and expensive?

The author has not previously submitted renal biopsy samples for prognostic purposes although is aware of US-based veterinary hospitals where renal biopsies are obtained very early on and results are used, clearly along with clinical progression, to guide duration of renal replacement therapy and recommendations regarding euthanasia.

Treatment

In patients at risk of AKI, prompt intervention may either avoid its occurrence or at least minimise its severity and progression. Treatment essentially comprises:

- Treating or preventing further exposure to the cause
- Supportive therapies
- Minimising further risk of kidney injury e.g. discontinue any medications with nephrotoxic potential; prevent further hypoperfusion/dehydration

Treating or preventing further exposure to the cause:

This may involve e.g.

Correct perfusion and hydration status
Patients exposed to nephrotoxins should be managed appropriately with gastrointestinal decontamination, fluid therapy and antidotes as indicated/available
If bacterial pyelonephritis is considered possible (e.g. based on clinical findings or active urine sediment), start broad-spectrum antibiosis (e.g. amoxicillin-clavulanate) until urine culture results received
If leptospirosis is possible, start intravenous amoxicillin-clavulanate (or amoxicillin or ampicillin) until test results received – this agent will reduce multiplication, shedding and transmission

- Then switch (e.g. after 10-14 days) to oral tetracyclines (e.g. doxycycline) or fluoroquinolones to eliminate carrier state

Supportive therapies:

As mentioned above, most veterinary patients with AKI are diagnosed during the maintenance phase when azotaemia is detectable. When presented with a patient with AKI, a main priority is to establish the patient's urine production status – is the patient oliguric, severely oliguric/anuric, or indeed polyuric and in the recovery phase?

Many patients with AKI present with existing **fluid deficits** which may be predominantly extravascular (dehydration) or with a significant intravascular component (hypovolaemia) as well. Fluid deficits need to be replenished according to standard principles before urine output can reliably be determined; continued provision for maintenance requirements and on-going losses is also essential. It is not possible to draw reliable conclusions about either urine output or the true severity of azotaemia until correction of fluid deficits has been achieved; persistent fluid deficits may also exacerbate AKI further. Initial fluid therapy should be aggressive if hypovolaemia is present and more conservative for rehydration. A replacement isotonic crystalloid solution is typically used alone.

Once fluid deficits have been replenished the patient should receive a fluid rate that is equal to urine production with maintenance provision and on-going losses provided *in addition.* Placement of an in-dwelling urethral catheter attached to a collection system is ideal for reliable measurement of urine production if possible, and will allow fluid therapy ('ins') to be matched to urine production ('outs'). It will also make it much easier to determine whether the patient is oliguric, anuric or polyuric. However patients should not be sedated/anaesthetised for catheter placement until/unless they are stable enough. Body weight is also useful for monitoring fluid status.

In an adult patient without existing fluid deficits, oliguria means urine output less than 0.5-1.0 ml/kg/hour; the range is because 'normal' urine output varies between individual patients based on e.g. breed, age. Patients that are severely oliguric or anuric will inevitably become fluid overloaded if maintenance requirements and provision for on-going losses continue to be administered without adequate urine production. However this is essential information in guiding further management and fluid therapy should not be withheld until there is evidence of overload. Being more cautious is justified in patients in whom there is concern for heart disease (e.g. heart murmur, gallop sound or known cardiac history), i.e. patients that are even more vulnerable to developing fluid overload with potentially life-threatening consequences, especially pulmonary oedema.

NO SUCH THING AS A STANDARD FLUID PRESCRIPTION SUITABLE FOR ALL CASES

Signs of **fluid overload** include:

- Chemosis
- Peripheral (e.g. hock) and facial (especially intermandibular) subcutaneous oedema
- Serous nasal discharge
- (Retro)peritoneal or pleural effusion
- Tachypnoea and later dyspnoea with harsh lung sounds and possible crackles due to pulmonary oedema

Diuretics are used in patients with inadequate urine production and furosemide (loop diuretic) is typically tried first. However it is essential to realise that diuretics are not therapeutic with respect to the AKI itself; rather they are a management tool that tries to promote urine production to prevent/resolve fluid overload thereby buying the patient time while the kidneys hopefully regain adequate function. Diuretics are only indicated if adequate fluid therapy fails to restore satisfactory urine output. Dialysis (peritoneal or haemodialysis) is indicated if fluid therapy and diuretic administration are unable to establish sufficient urine output such that fluid overload occurs/cannot be resolved.

Furosemide may be used as bolus therapy (e.g. 0.5-1.0 mg/kg IV every 8 hours) or as a constant rate infusion (e.g. 0.5-1.0 mg/kg IV bolus then 0.5-1.0 mg/kg/hour CRI); the latter may be more rational but at the present time a supportive clinical evidence base is lacking.

Higher doses may be tried if these doses do not achieve a positive effect. Mannitol (osmotic diuretic)(e.g. 0.5-1.0 g/kg IV over 15-20 minutes every 4-6 hours; or 1-2 mg/kg/minute CRI) has also been used in AKI management, often following or together with furosemide. If a positive response is not seen to the first bolus dose, do not give any more. If there is no positive response after 1 hour of CRI administration it should be discontinued. Mannitol is contraindicated in anuric patients or oliguric patients with existing signs of fluid overload as it may worsen hypervolaemia leading to pulmonary oedema and possible congestive heart failure. The use of dopamine is not recommended in AKI treatment in human medicine and likewise in veterinary medicine. There is no evidence for a beneficial effect in dogs or cats with AKI and potential adverse effects exist; the risk-benefit assessment is therefore neutral or on the side of risk without benefit.

Some patients with AKI may present with or go on to develop clinically significant hyperkalaemia as a result of reduced urinary excretion; this should be addressed according to standard principles and in some cases is the initial priority following presentation.

Ultimately if a patient cannot be kept stable without life-threatening fluid overload and hyperkalaemia, i.e. the patient fails medical management, then renal replacement therapy (peritoneal dialysis, intermittent haemodialysis or continuous renal replacement therapy) is indicated. This therapy again is not therapeutic in terms of the AKI itself but buys time to see whether the kidneys will regain adequate function to allow the patient to return to a reasonable quality of life. If RRT is not available or affordable then euthanasia is indicated. Furthermore it is essential to realise that RRT is not an appropriate intervention in all patients with AKI and each patient should be considered on their individual merit and circumstances. RRT also has some risks and potential complications, is costly and still has limited availability in veterinary medicine.

Other therapies that should be considered to address complications of uraemia include:

- Anti-hypertensives: systemic hypertension is common in AKI and is not correlated to the severity of azotaemia. Depending on the severity, oral (e.g. amlodipine; an ACE inhibitor) or parenteral (e.g. hydralazine; sodium nitroprusside) therapy may be needed.
- Antiemetic/anti-nausea medication (e.g. maropitant; metoclopramide)
- Antacids (e.g. omeprazole)
- Analgesia if renal pain is suspected
- Nutritional support: anorexia is common and in patients that are tolerant, enteral nutrition via feeding tube (typically naso-oesophageal in these patients) should be considered.

The conversion from oliguria/anuria to polyuria is encouraging and the simplest indicator of potential recovery available. The use of urinary sodium fractional clearance* has also been described in a study of a very small number of dogs as a way of detecting renal functional recovery.

[*The fractional excretion of sodium is the percentage of the sodium filtered by the kidney which is excreted in the urine. It is measured in terms of plasma and urine sodium, rather than by the interpretation of urinary sodium concentration alone, as urinary sodium concentrations can vary with water reabsorption. Therefore the urinary and plasma concentrations of sodium must be compared to get an accurate picture of renal clearance.]

Patients may be profoundly polyuric in the *recovery* phase which may result in fluid deficits and electrolyte abnormalities such as hypokalaemia and hypernatraemia without close monitoring and intervention. These animals are unable to concentrate their urine in the face of inadequate fluid intake and will become dehydrated. Once the patient is stable, eating and drinking, and the azotaemia has resolved or at least plateaued, intravenous fluid therapy is slowly tapered (e.g. by 10-25% daily) with continued close monitoring of urine production, creatinine and hydration status. Ideally urine production reduces in tandem with reduced fluid therapy and azotaemia does not worsen allowing fluid therapy to continue to be weaned.

Prognosis:

Despite some publications of potential prognostic models, it is difficult to comment reliably on the prognosis associated with AKI. In general outcome is largely dependent on the underlying cause (e.g. grave with ethylene glycol intoxication unless antidotal therapy is started early) and the severity of disease, with existing comorbidities also playing a role. The lack of clarity largely stems from the fact that the availability of renal replacement therapy clearly has the potential to significantly affect outcome in individual patients and this needs to be clarified when prognosticating. Even without RRT, the ability of a practice to provide 24-hour intensive expert care is likely to also influence outcome to some degree and client preferences and euthanasia are always difficult to account for in veterinary medicine when prognosticating on an individual patient basis.

Animals that survive to discharge are likely to retain a degree of azotaemia, which may or may not then fully resolve over the subsequent weeks.

Nothing can be done about the renal injury that animals presenting with AKI will already have suffered; in some cases, recovery will not occur despite aggressive therapy that may or may not include dialysis. However, the chances of a successful outcome are maximised by early and intensive treatment and close monitoring. If not precluded by financial constraints, the author would strongly recommend the referral of dogs and cats with AKI for specialist care if optimal management cannot be provided within the primary clinic.